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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER

ART UNIT	PAPER NUMBER
	7

DATE MAILED:

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 8/17/93 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-40 are pending in the application.
   Of the above, claims 21-27, ~~30~~ 31, ~~32~~ 35 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-20, 28-~~29~~ 31, 33, 34, 36-40 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☒ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☒ been received ☐ not been received ☒ been filed in parent application, serial no. 07/946,448; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

15. Claims currently under consideration are 1-20, 28-29, 32, 33, 34, and 36-40. Claims 21-27, 30-31, and 35 stand withdrawn from consideration. Applicants' request to hold the drawing requirements in abeyance until such time as allowable subject matter is identified is noted. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior office action. The location of this application has changed. All future correspondence regarding this application should be sent to the Examiner's attention with art unit designation 1816. Current fax and telephone contact numbers may be found at the end of this Office Action.

16. Claims 1-20, 28-29, 32-34, and 36-40 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent 5,354,844 view of Wu et al., (AC1), Knapp et al., Goers et al. ('973), Hirsch et al. ('132) and Rossi et al. Applicant's traversal appears to be over the following grounds: 1) The claims of the 'application do not suggest the claims of the instantly claimed invention, and 2) "... the Examiner provides nothing more than a broad series of suggestions "to try" a great variety of possibilities, and 3) the Examiner has provided no motivation to introduce nucleic acids into T-cells. Applicants' traversal has been considered but is not found persuasive for the following reasons. In the establishment of an obviousness-type double patenting rejection, the Examiner must make a determination on who represents those skilled in the art. In the case of the instant invention, it would be those individuals who engage in the production of transfection vehicles such as the claimed protein-polycation complexes and use such vehicles in the transfection of cells. Accordingly, the determination of the Examiner is that one of ordinary skill in the art would recognize that where the introduction of nucleic acids, such as ribozymes, into T-cells is desired, one of ordinary skill would necessarily utilize proteins, such as gp120 or antibodies to T-cell proteins known to be capable of initiating endocytosis, in order to facilitate the introduction of DNA into the target cells, especially in view of the Hirsch et al. patent which specifically suggests the use of antibodies to target DNA to T-cells for the purposes of transformation or to introduce exogenous DNA sequences in to the cells through the internalization (endocytosis) of the antibody-nucleic acid conjugate (see Detailed Description and Example 3). It is the target cell that dictates what the targeting agent will be, this is a fact that would have been readily recognized by the routineer (see Hirsch et al., entire document, especially column 4, lines 20-68). Furthermore, it was known in the art that CD4 and CD7 specific antibodies were capable of inducing endocytosis into T-cells (see Carriere et al.). In view of the teachings of the references, it would have been prima facie obvious to one of ordinary skill in the art to substitute antibodies for the transferrin targeting agent of the '844 patent. For these reasons, Applicants' arguments have not been found persuasive.

17. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling

disclosure and failing to present the best mode contemplated by the applicant for carrying out the invention. The specification is objected to for the following reasons:

A) The specification is objected to, and claim 38 is rejected, under 35 USC 112, first paragraph as the specification fails to enable and teach one skilled in the art how to use the claimed pharmaceutical compositions as a therapeutically effective agent. Applicants have not disclosed how to use the claimed compositions, complexes, and processes therapeutically in humans. Claims drawn to pharmaceutical compositions are viewed as therapeutic agents. Factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented in the specification, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breadth of the claims (see Ex parte Forman, 230 USPQ 546, BPAI, 1986). While the level of skill in the art is high, the state of the art with respect to gene therapy protocols reflects the high degree of unpredictability currently recognized in the art with respect to such treatment protocols (see recognitions of such unpredictability in the art in the article published in the Washington Post, December 1995). Furthermore, no working examples are of record and no evidentiary showing has been made with respect to the use of the claimed pharmaceutical compositions in an in vivo setting.

The specification provides in vitro examples for the transfection of cells with the claimed conjugates, however is well known in the art that correlation between in vitro assays and in vivo animal studies to in vivo human efficacy is a major barrier. Harris et al. states that there is widespread acceptance that there is little future for the use of rodent monoclonal antibodies for in vivo human therapy (page 42, column 2) and that repeated dosing with chimeric antibodies is ineffective due to residual anti-idiotypic responses (page 42, column 3). Applicant's compositions and processes do not utilize targeting agents which would be recognized as self by the human immune system. The invention appears to rely on the use of murine monoclonal antibodies and as is indicated in Harris et al., such antibodies lose effectiveness after their initial use because of the human anti-mouse antibody (HAMA) response. Applicant also proposes the use of gp120 as the targeting agent for the conjugates of this invention. This protein, an admitted and art recognized antigen associated with the HIV virus would stimulate an immune response also resulting in its immunological inactivation in vivo. Anti-gp120 specific antibodies upon HIV infection are observed in HIV infected patients. Applicant also discloses that chloroquin is required to transfect cells in some instances. This is also an art recognized requirement of ensuring transfection (see Cotten et al. (AS1), page 4037, paragraph 2). Cotten et al. indicate that the cytotoxicity of chloroquin

would limit the use of the transfection system in vivo. While the treatment of T-cells could be undertaken in vitro (ex vivo), the HIV virus is known to infect a large variety of cells and organs including neurons and the liver and is found in localized foci such as lymph nodes and the administration of chloroquin would have deleterious effects on the patient.

18. Claims 1-8, 11-20, and 36-40 stand rejected under 35 U.S.C. § 103 as being unpatentable over Wu et al. (AC1) or Wagner et al. (AT2) in view of Goers et al. or Hirsch et al. ('132), Carriere et al., and Knapp et al. Claims 1-5, 7-8, and 11-16 are drawn to protein-polycation conjugates wherein the targeting component of the conjugate is a T-cell specific monoclonal antibody or a protein that specifically binds to a T-cell antigen such as CD4 (i.e. the HIV protein gp120). The claims are also drawn to the use of modified histones, histones, polylysine, protamine in the conjugates as the polycation substance. Claims 17-20 are directed to complexes comprising the conjugates of claim 1 with associated nucleic acids. Claims 36-37 are drawn to a process for the introduction of nucleic acids into T-cells through the use of the conjugates of claim 1. Wu et al. teach a method of transfecting hepatocytes using asialoproteins conjugated to polycations for the transfection of liver cells (see abstract and column 4, paragraph 2). Wagner et al. teach the use of transferrin-polycation conjugates for the transfection of cells with DNA including the use of polylysine and protamine. Wu et al. teach a number of polycationic molecules useful in the instant invention, including histones, polylysine, etc (column 4, paragraph 2). Wu et al. teach that other targeting agents (i.e. hormones or antibodies) may be used to direct the conjugates to the target cell (see columns 5-6, The nature of the Ligand) and that agent used will depend upon the target cell. The references do not teach the use of T-cell specific antibodies for the targeting of polycation-nucleic acid complexes into cells. Goers et al. teach that therapeutic agents are selected for their intended application. Where the targeting of therapeutic agents to T-cells is contemplated, antibodies specific for T-cell antigens would be selected. Furthermore, Hirsch et al. teach the use (a process of introducing DNA into T-cells) of T-cell specific antibodies to target nucleic acids to T-cells for transformation purposes in order to produce interleukins, etc. (see Example 3). Knapp et al. teach a variety of known T-cell specific antibodies which are commercially available. Carriere teaches that anti-CD4, CD7, and CD5 antibody conjugates are internalized by cells expressing these cell markers (see Abstract and Discussion). CD7 is an admitted tumor associated antigen (see specification, pages 12-13). The substitution of such antibodies as targeting agents of protein-polycation complexes would have ben obvious to one of ordinary skill where the targeting of T-cell was desired. Such targeting would be desired when one wished to treat T-cell leukemias or HIV infected T-cells or to induce the production of lymphokines (see Hirsch). The use of gp120 to target polycation-nucleic acid complexes to CD4 expressing cells would be functionally analogous to using anti-CD4 antibodies, and in view of the state of the art at the time of invention, an obvious means of targeting therapeutic agents to CD4 expressing cells in view of

the state of the art and the recognition in the art that the HIV virus was internalized into CD4 expressing cells through the interaction of gp120 with the CD4 molecule.

One of ordinary skill in the art at the time the invention was made would have been motivated to select and substitute T-cell specific antibodies or gp120 (for the transferrin molecule of Wu et al. or Wagner et al.) as the targeting agents for protein-polycation conjugates or complexes of said conjugates additionally containing nucleic acids because such antibodies would allow for the specific direction and introduction of nucleic acid laden conjugates to T-cells for the purpose of introducing foreign DNA into the cells for either therapeutic purposes or for the production of interleukins. One of ordinary skill in the art would have also been motivated to transfect T-cells through the contacting of T-cell markers with T-cell antibody specific DNA conjugates in o From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

19. **RESPONSE TO TRAVERSAL:** Applicants' arguments have been considered but are not found persuasive for the following reasons. Applicant traverses on the grounds that the combination of references fails to teach or suggest the combination of references. It is what the combination of references teaches to one of ordinary skill and a determination of who one of ordinary skill was at the time of invention which renders the claimed invention obvious. As stated earlier, the determination of the routineer for the purposes of this invention is held to be one who constructs and uses protein polycation complexes in transformation techniques. At issue in the instantly claimed invention is the following: Is Applicants' invention, namely proteins which are able to deliver nucleic acids specifically into T-cell rendered obvious to those skilled in the art based on the combination of references and in view of the skill level at the time of invention? It is the position of the Examiner that the combination renders the invention obvious for the following reasons: 1) The art recognized the potential of nucleotide analogues for the treatment of a variety of diseases, including HIV infection (see Applicants' admitted prior art Zon et al., especially pages 545-546) and 2) Antibodies which specifically directed materials into T-cells were known in the art well before the earliest priority date of Applicant (see Calliere et al.). Those skilled in the art are presumed to be familiar with any and all references related to the claimed invention and the question of obviousness remains that do the combined references suggest the invention to one of ordinary skill in the art at the time of invention. Where the routineer sought to introduce nucleic acids into T-cells, it is the position of the Examiner that the combination does, in fact, render the claimed invention obvious, especially in view of the Hirsch reference. In response to Applicants' argument that the Examiners conclusion of obviousness is based upon

improper hindsight reasoning, it must be recognized that any judgement on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the Applicants' disclosure, such a reconstruction is proper, In re McLaughlin, 443 F.2d 1392; 170 USPQ 209 (CCPA 1971).

20. Claims 17, 20, 28-29 and 32-34 stand rejected under 35 U.S.C. § 103 as being unpatentable over Wu et al. (AC1) or Wagner et al. (AT2) in view of Goers et al., Hirsch et al. ('132), Knapp et al., and Carriere et al., as applied above and further in view of Haseloff et al., or Rossi et al. ('019) and Applicants' admitted prior art regarding oncogene inhibitory nucleic acids (see page 26, paragraph 3 of the specification). The teachings of the Wu et al. (AC1), Wagner et al. (AT2), Goers et al., and Hirsch et al. ('132) references have been discussed above. Claims 28-29 and 33-34 are drawn to protein-polycation/nucleic acid complexes wherein the nucleic acid is a ribozyme which an inhibitory nucleic acid or an oncogene inhibitory nucleic acid and the targeting component of the conjugate is a T-cell specific monoclonal antibody or a protein that specifically binds to a T-cell antigen such as CD4 (i.e. the HIV protein gp120). Wu and Wagner differ from the claimed invention in that the use of antibody targeting agents and nucleic acids comprising ribozymes are not taught. Therapeutic agents of the gene therapy category also include ribozymes. Haseloff et al. teach ribozyme enzymes (ribozymes) and a variety of applications for these molecules (see pages 590-591) such as the specific targeting of a particular gene RNA transcript with ribozymes. The "anti-gene activity" of ribozymes is indicated to provide a basis for gene therapy of various diseases, including HIV infection (column 1, '019). This section also indicates that transfection or transformation techniques to introduce genes encoding ribozymes into various types of cells were known in the art in 1988. Those skilled in the art would have been able to insert ribozymes into a variety of genetic constructs in order to facilitate the expression of the ribozyme of a desired specificity. Rossi et al. teach ribozymes capable of cleaving HIV-1 RNA and provide a variety of therapeutic applications for the disclosed ribozymes of their invention. Included in this teaching is that therapeutic ribozymes may be introduced into cells by a variety of methods including the transfection of cells with DNA encoding the ribozymes of a desired specificity (see column 6, Therapeutic Procedures). Ribozymes are also taught to be capable of inactivating endogenous RNA transcripts including those produced by the ras, myc, or src oncogenes. Ribozyme contained within tRNA transcripts are known in the art (see specification, page 19). In view of the teachings of Rossi et al. and/or Haseloff et al., one of ordinary skill would have recognized that the targeting of ribozymes to T-cells expressing oncogene proteins or HIV proteins using polycation-protein conjugates such as those taught by Wagner et al. would have been useful for inactivation of the genetic transcripts contained within the cells. Further, one of ordinary skill would have recognized, prior to Applicant's earliest priority date, that the targeting

specificity of the system disclosed by Wagner et al. could be greatly enhanced by the use of antibodies to specifically target therapeutic agents such as ribozymes.

One of ordinary skill in the art at the time the invention was made would have been motivated to select and substitute T-cell specific antibodies or gp120 (for the transferrin molecule of Wu et al. or Wagner et al.) as the targeting agents for protein-polycation conjugates or complexes of said conjugates additionally containing nucleic acids because such antibodies would allow for the specific direction and introduction of ribozyme laden conjugates to T-cells for the purpose of introducing foreign nucleic acids, such as ribozymes, into the cells for the inactivation of RNA contained with the cells. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

21. **RESPONSE TO TRAVERSAL:** Applicants' traversal covers, essentially, the same ground as that in the previous traversal on the first 103 rejection set forth by the Examiner. Applicants' arguments have been considered but are not found persuasive for the following reasons: 1) Applicants' traversal on the arguments presented in the first 103 rejection (above) are not found persuasive for the reasons set forth above in paragraph #*******) Applicant argues that there is no motivation to target ribozymes to T-cells based on the combination of references. Again, it should be pointed out that what would reasonably have been known and used by one of ordinary skill in the art need not be explicitly taught with regard to the claimed material, In re Nilssen, 851 F.2d 1401, 7 USPQ2d 1500 (Fed. Cir. 1988). Ribozymes were known to be capable of degrading the mRNA of a variety of genes. Haseloff et al. teach that synthetic ribozymes can be constructed to inactivate the RNA of any particular gene, given that the sequence is known (see pages 591-592). Rossi et al. teach that HIV-1 specific ribozymes were known before the time of the invention of the claimed subject matter. In view of the combined references, it is the conclusion of the Examiner that one could reasonably expect to arrive at the claimed invention because those skilled in the art recognized the usefulness of introducing ribozymes into target cells and also recognized and knew those antibodies useful in targeting materials into T-cells. The construction of proteins-polycation conjugates according to the claimed invention was within the skill level of the routineer and one of ordinary skill would have been motivated to construct such products because they would have been useful for the introduction of nucleic acids into cells in a manner directly analogous to that of Wu et al. or Wagner et al. Applicants' arguments have been considered but are not found persuasive.

NEW GROUNDS OF REJECTION

22. Claims 1 and 9-10 are rejected under 35 U.S.C. § 103 as being unpatentable over Wu et al. (AC1) or Wagner et al. (AT2) in view of Goers et al. and Knapp et al. and Calliere et al., as applied above (see paragraph 18) and further in view of Goding et al. Claims 1 and 9-10 are drawn to compositions comprising antibodies bound to polycations through protein A antibody interactions. The teachings of the references have been discussed in paragraph 18 and differ from the claimed invention in that the binding attachment of polycation to antibody through a protein A-antibody interaction is not taught in the combination of references. Goding et al. teach that protein A may be used as an immunological reagent for the attachment of reagents to antibody molecules. Specifically, the attachment of labels such as fluorescein or radioisotopes to cell bound antibodies is taught by the reference (see page 248). In view of the art recognition that labels such as fluorescein or radioisotope could be, and were, attached to antibodies through a protein A-antibody interaction, it would have been obvious to one of ordinary skill in the art that polycations could also be attached to antibodies through the protein A-antibody interaction, thereby providing a means of attaching DNA to antibodies or facilitate the isolation of antibodies through ion exchange chromatography.

One of ordinary skill in the art at the time the invention was made would have been motivated to select make an antibody-protein A-polycation compound because such proteins would have allowed for the specific direction and introduction of nucleic acid laden conjugates to T-cells or facilitated the isolation of such antibodies through ion exchange chromatography. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

23. No claim is allowed.

24. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher Eisenschenk whose telephone number is (703) 308-0452. The examiner can normally be reached Monday through Thursday from 6:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. The fax phone number for Group 180 is (703) 305-3014 or (703) 305-7401. Any inquiry of a

general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

C. Eisenschenk

February 26, 1996
Christopher Eisenschenk, Ph.D.
Patent Examiner
Group 1800